weeks), while those with unchanged or increased levels were between 1-3 weeks (mean: 2.0 ± 0.6 weeks, p = 0.06) following LVAD treatment. TIMP-1 and TIMP-4 transcript levels increased in 4 and decreased in 3 patients. Changes in gene expression of those two transcripts correlated positively with each other during LVAD support (r2: 0.9, p < 0.001). There was no correlation between TIMP expression and time on support, and there was no reciprocal change in MMP expression.
Conclusions: Myocardial gene expression of MMP-1, MMP-9, TIMP-1, and TIMP-4 do not change predictably during LVAD treatment, with the exception of MMP-9, which decreased after 3 weeks. These findings suggest a non-linear or biphasic response of MMP-9 expression with mechanical unloading. In addition, the positive correlation between changes in transcript levels of TIMP 1 and 4 suggest a common transcriptional mechanism.

4:30 p.m.

876-3 Expression Profiling of Genes in Eight Failing and Seven Nonfailing Human Hearts by Oligonucleotide Microarrays

Fen-Lai Tan, Christine S. Moravec, Jianbo Li, Carolyn Apperson-Hansen, Patrick M. McCarthy, James B. Young, Meredith Bond, *The Cleveland Clinic Foundation, Cleveland, Ohio.*

Background: Systematic expression profiling of genes at the global level in multiple human hearts in order to generate a complete complement of heart failure genes, has not been reported to date.
Methods: Using oligonucleotide microarrays (Hu-6800, Affymetrix. Inc, CA), complementary RNA isolated from left ventricular free wall of 7 non-failing (NF) and 8 failing human (FH) hearts (diagnosis: idiopathic dilated cardiomyopathy) was profiled for gene expression. Using Wilcoxon Rank-Sum test (P<0.05) and Student's T-test after log-transformation (P<0.05), 1145 out of ~7000 genes on the chip that are potentially differentially expressed between NF and FH hearts was generated. After elimination of genes with <1.5 fold change in expression level, 387 remained significant. To minimize the likelihood of false positives, a minimum mean average difference of 200 units was imposed. Of the 387 genes, this additional cut-off point generated 115 genes with increased expression and 74 genes with decreased expression in the FH hearts. This comprehensive cut-off point is being confirmed by quantitative PCR.
Results: 189 genes in 10 clusters were found differentially expressed between the NF and FH hearts. As validation of this approach, changes in expression of a number of these genes are well documented, e.g. biomarkers for heart failure (ANF, BNP, troponin T1) were significantly increased, and several contractile proteins (e.g. a cardiac actin, myosin light chain) were significantly decreased. However, the majority of the genes have not previously been reported, e.g. up-regulated human brahma-related gene-1 (BRG1, the ATPase subunit of SWI/SNF, involved in MyoD-mediated muscle differentiation) and thrombospondin-4 (an extracellullar Ca2+-binding adhesion protein, associated with increased risk of early heart attack); down-regulated metallothionein (an inhibitor of the MAP kinase pathway, involved in resistance of Doxorubicin cardiotoxicity) and anti-chymotrypsin (a proteinase inhibitor, reported to attenuate myocardial ischemic injury).
Conclusions: Novel findings include changes in expression of genes with a potential role in cardiac remodeling.

4:45 p.m.

876-4 Microarray Analysis of Changes in Gene Expression Following LVAD Support

Nicholas R. DiPaola, Nicholas G. Smedira, Patrick M. McCarthy, James B. Young, Christine S. Moravec, *Cleveland Clinic Foundation, Cleveland, Ohio.*

Data from our laboratory and others suggest that mechanically unloading the failing human heart with a left ventricular assist device (LVAD) results in improved muscle function and altered gene expression. Although provocative, such studies fail to address the interaction between genes or the possibility that groups of genes are coordinately regulated. We studied paired tissue samples from four patients before and after LVAD, using the Affymetrix Microarray system to simultaneously measure expression of 7000 genes. Patients were male, between 35 and 55 years of age, and had dilated cardiomyopathy. Duration of LVAD support was short (35 days) in two patients, and long (135 days) in two patients. Total RNA was prepared from tissue removed during LVAD implant and at transplant in all patients. RNA samples were reverse transcribed and *in vitro* translated into biotinylated cRNA, which was hybridized to Affymetrix human gene chip arrays. Analysis revealed the presence of 3476 genes, of which 196 were changed following LVAD support in at least three of the patients (69 genes), or were differentially regulated by duration of support (97 genes). Significant changes in gene expression in all four patients following mechanical unloading included a 4.5 fold decrease in atrial natriuretic factor and a 5.3 fold decrease in phospholipase A2, as well as an 11.0 fold increase in in c-fos, a 4.3 fold increase in plasminogen activator inhibitor-1, a 3.4 fold increase in a zinc finger transcriptional repressor of TNF, and a 2.7 fold increase in protein tyrosine phosphatase. Genes which were differentially regulated based on duration included a 2.6 fold increase in GATA-4 in short duration patients, with no change following long duration support, as well as no change in protein phosphatase 2A during short term support, but a 2.0 fold increase following longer durations. Although much data remains to be analyzed, and the functional significance of these changes remains to be explored, the analysis of paired samples from LVAD-supported patients using Microarray techniques is a powerful approach for elucidating the coordinate changes in gene regulation following hemodynamic unloading of the failing human heart.

ORAL CONTRIBUTIONS

879 Cardiogenic Shock and Assist Devices

Tuesday, March 19, 2002, 4:00 p.m.-5:00 p.m.
Georgia World Congress Center, Room 367W

4:00 p.m.

879-1 Reversal of Cardiogenic Shock by Left Atrial-to-Femoral Arterial Bypass Assistance

Holger Thiele, Bernward Lauer, Enno Boudriot, Angela Genov, Rainer Hambrecht, Gerhard Schuler, *University of Leipzig - Heart Center, Leipzig, Germany.*

Background: Mortality in cardiogenic shock following acute myocardial infarction remains at an unacceptable level despite interventional treatment of the underlying cause and use of intraaortic balloon counterpulsation. Frequently patients succumb to low cardiac output before the myocardium is able to recover from the ischemic event. A newly developed left ventricular assist device (Tandem Heart pVAD, Cardiac Assist Technologies, Inc., Pittsburgh, Pennsylvania, USA) with active circulatory support might decrease mortality.
Methods and results: Between 05/2000 and 09/2001 in 19 consecutive patients with cardiogenic shock a percutaneous left atrial-to-femoral arterial bypass assist device was implanted. The device was connected to the patients' circulation by transseptal puncture of the left atrium; blood was returned to the iliac artery through an arterial cannula. In 13 patients cardiogenic shock was caused by an acute myocardial infarction and in 6 by an infarct related ventricular septal defect. Mean duration of cardiac assist was 4±3 days. Mean flow of the device was 3.3±0.6 l/min. Before support cardiac index was 1.7±0.3 l/min/qm and improved to 2.4±0.6 l/min/qm (p<0.001) with cardiac assist. Mean blood pressure increased from 64±8 mmHg to 80±9 mmHg (p<0.001). Pulmonary capillary wedge pressure, central venous pressure and mean pulmonary artery pressure were reduced from 20±5, 12±4 and 31±8 mmHg to 14±4, 9±3 and 23±6 mmHg (all p<0.01), respectively. Overall mortality was 42%.
Conclusion: In patients with cardiogenic shock hemodynamic parameter can be substantially enhanced by use of a percutaneous left atrial-to-femoral arterial assist device. It provides up to 4.0 l/min of additional cardiac output, which is sufficient to revert cardiogenic shock in most patients. By diverting blood from the left atrium the left ventricular myocardium is unloaded, making recovery more likely following an ischemic event. The influence of this device on long-term prognosis warrants further investigations.

4:15 p.m.

879-2 The Paraaortic Counterpulsation Device Implanted on the Ascending Aorta Is Superior to an Equal Volume Intraaortic Balloon Pump: Experimental Study

John Terrovitis, Christos Charitos, Paraskevi Dolou, Argyrios Ntalianis, Stavros Drakos, Charalampos Pierakos, Kostas Chalkias, Panagiotis Papazoglou, John Nanas, *Department of Clinical Therapeutics, University of Athens, Athens, Greece.*

Backround:We aimed to compare the hemodynamic effects of a 40ml total volume paraaortic counterpulsation device (PACD, stroke volume 30ml) to those of a 40ml intraaortic balloon pump (IABP), in an acute experimental porcine model of heart failure.
Methods: In 6 pigs, weighting 53 to 64kgr, left ventricular failure was induced with multiple ligations of small coronary arteries and propranolol and amiodarone infusion. The IABP was placed into the descending aorta and the PACD was implanted in the ascending aorta via a 3cm vascular graft. Aortic pressures were recorded with and without mechanical assistance, provided by the IABP and the PACD, alternately. Cardiac output was monitored using a transit time ultrasound flowmeter placed on the pulmonary artery. Double Product (DP), Tension Time Index (TTI), Diastolic Pressure Time Index (DPTI) and Endocardial Viability Ratio (EVR) were calculated. Both devices were driven by the Datascope 96 driving system.
Results: The hemodynamic effectiveness of the devices was evaluated from their ability to reduce the afterload of the left ventricle and to provide diastolic aortic augmentation. Both significantly reduced the systolic aortic pressure (from 112 ± 18mmHg to 100 ± 17, p=0.000, and to 98 ± 23, p=0.000, using the IABP and the PACD, respectively) and the end diastolic aortic pressure, (from 82 ± 17mmHg to 74 ± 19, p=0.000 and to 50 ± 22, p=0.000, respectively). The PACD reduced the end diastolic aortic pressure more than the IABP (reduction of 42.6 ± 18.1% vs 11.0 ± 9.9%, p=0.000). The counterpulsation wave of the PACD was significantly greater than that of the IABP (augmentation of 44.8 ± 22.2% vs 37.6 ± 15.6%, p=0.031). Both devices significantly lowered the end diastolic left ventricular pressure, DP and TTI and increased cardiac output, DPTI and EVR comparably.
Conclusion: Both devices showed significant hemodynamic effects in left ventricular function. Although the PACD was of a smaller stroke volume, it provided greater salutary hemodynamic effects. The simplicity of the implantation procedure of the PACD and the ability to be driven by the standard IABP driving system make it a promising device for wide use for mechanical assistance of the failing heart.